CLINICAL STUDY REPORT

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| Study Title: | A Two Part Study to Assess the Safety, Pharmacokinetics and Pharmacodynamics of SBT-020 in Patients with Early Stage Huntington’s Disease |
| Investigational Product: | SBT-020 |
| Indication Studied: | Early stage Huntington’s Disease |
| Description of Study: | Part 1: A randomized, double-blind, placebo-controlled, repeat dose study of SBT-020 (5 mg, 15 mg or 25 mg) administered subcutaneously for 7 days, assessing the safety and pharmacokinetics of study medication in patients with early stage Huntington’s Disease.  Part 2: A randomized, double-blind, placebo-controlled, repeat dose study of SBT-020 (25 mg) administered subcutaneously for 28 days, assessing the safety, pharmacokinetics and pharmacodynamics of study medication in early stage Huntington’s Disease. Pharmacodynamics were primarily assessed through mitochondrial function by analysis of phosphocreatine recovery time during 31P-MRS and in PBMCs. Additional pharmacodynamic endpoints in neurocognitive, motor function and UHDRS were assessed. |
| Name of Sponsor: | Stealth BioTherapeutics Inc. |
| Protocol Number: | SBT20-102 |
| EudraCT Number: | 2016-003730-25 |
| Toetsing Online Number: | NL59198.056.16 |
| Development Phase: | Phase 1/2 |
| First Subject Enrolled: | 14 April 2017 |
| Last Subject Completed: | 21 December 2017 |
| Principal Investigator: | G.J. Groeneveld, MD, PhD  Centre for Human Drug Research  Zernikedreef 8 Leiden 2333 CL, the Netherlands |
| Sponsor Signatory: | Jim Carr, PharmD  Chief Clinical Development Officer  Stealth BioTherapeutics, Inc.  140 Kendrick St., Building C-West  Needham, MA 02494 |
| GCP Compliance: | This study was performed in compliance with International Council for Harmonisation (ICH) Good Clinical Practices (GCP), including the archiving of essential documents as well as the ethical principles of the Declaration of Helsinki |
| Report Version and Date: | Final, 05 October 2021 |

CONFIDENTIAL

# Synopsis

| **Name of Sponsor/Company: Stealth BioTherapeutics Inc.**  **Name of Investigational Medicinal Product: SBT-020**  **Study Number: SBT020-102** | |
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| **Title of Study:**  A Two Part Study to Assess the Safety, Pharmacokinetics and Pharmacodynamics of SBT-020 in Patients with Early Stage Huntington’s Disease | |
| **Principal Investigators:**  G.J. Groeneveld, MD, PhD | |
| **Study Center:**  Centre for Human Drug Research (CHDR), Zernikedreef 8 Leiden 2333 CL, the Netherlands | |
| **Publication (Reference):**  Marcus P.J. van Diemen, Ellen P. Hart, Anthony Abbruscato, Liz Mead4, Ilse van Beelen, | Sandrin C. Bergheanu, Pieter W. Hameeteman, Emma Coppen, Jessica Y. Winder, Matthijs Moerland, Hermien Kan, Jeroen van der Grond, Andrew Webb, Raymund A.C. Roos, Geert Jan Groeneveld  Safety, pharmacokinetics and pharmacodynamics of SBT-020 in patients with early stage Huntington's disease, a 2-part study  Br J Clin Pharmacol. 2020;1–13. | |
| **Study Period:**  First subject, first dose: 14 Apr 2017  Last subject, last visit: 21 Dec 2017 | **Phase of Development:**  1/2 |
| **Background and Rationale for the Study:**  Huntington’s disease (HD) is an autosomal dominant inherited neurodegenerative disorder characterized by a triad of symptoms including motor disturbances, cognitive dysfunction and psychiatric symptoms. There is strong evidence that mitochondrial dysfunction is Part of the pathogenesis of HD. Pharmacologically inhibiting succinate dehydrogenase in rodent and primates, thereby inhibiting complex II of the mitochondrial electron transport chain, resulted in pathology and symptomatology resembling HD. Furthermore, in vitro research has shown that mutant huntingtin inhibits the import of nuclear coded mitochondrial proteins and down regulates the activity of peroxisome-activated receptor gamma (PPARɣ), required for mitochondrial biogenesis. Using in vivo 31 phosphorus Magnetic Resonance Spectroscopy (31P-MRS) in the calf muscles it has been shown that HD patients exhibit a prolonged phosphocreatine (PCr) recovery time (τPCr) compared to healthy controls, which can be translated into a declined mitochondrial function in HD patients. Mitochondrial function in the brain, measured by levels of PCr and inorganic phosphate (Pi) before, during, and after a visual stimulus, also has been shown to be impaired in HD patients. In healthy controls, an increase in the Pi/PCr ratio was shown to be induced by visual stimulation (indicating a normal bioenergetics profile), but the healthy subject response was not present in HD patients. Improving mitochondrial function in HD patients might therefore be beneficial for delaying disease progression by maintaining the energy level inside the striatum cells and thus preventing cell death.  SBT-020 is an experimental mitochondrial function enhancing agent, which has showed promising results in pre-clinical animal models. While the exact mechanism of action is not completely understood, it is hypothesized that the compound can improve the mitochondrial function in HD patients, thereby slowing neuronal degeneration and disease progression. The pharmacokinetics, safety and tolerability of SBT-020 have been evaluated in a first-in-man study and SBT-020 was well tolerated in all dose levels investigated. There is no information yet on efficacy in humans. | |
| **Objectives:**  **Part 1**  **Primary:**  To assess the safety and tolerability of SBT-020 in early stage HD patients.  **Secondary:**   1. To investigate the effect of SBT-020 on mitochondrial function, measured by dynamic 31P-MRS in the calf muscles of early stage HD patients. 2. To assess the pharmacokinetics of SBT-020 and SBT-020-related component (SBT-127) in plasma in early stage HD patients. 3. To assess the pharmacokinetics of SBT-020 and SBT-020-related components (SBT-127 and SBT-098) in urine in early stage HD patients. 4. To investigate the effect of SBT-020 on mitochondrial function, by measuring the mitochondrial membrane potential (MMP) in isolated peripheral blood mononuclear cells (PBMCs).   **Part 2**  **Primary:**  To assess the safety and tolerability of longer-term treatment with SBT-020 in early stage HD patients.  **Secondary:**   1. To investigate the effect of SBT-020 on mitochondrial function, measured by dynamic 31P-MRS in the calf muscles of early stage HD patients. 2. To investigate the effect of SBT-020 on the bioenergetic profile, measured by 31P-MRS in the brain of early stage HD patients. 3. To assess the pharmacokinetics of SBT-020 and SBT-020-related component (SBT-127) in plasma in early stage HD patients. 4. To investigate the effect of SBT-020 on mitochondrial function, by measuring the MMP in isolated PBMCs. 5. To investigate the effect of SBT-020 on an exploratory set of urinary and plasma biomarkers related to mitochondrial function in early stage HD patients. 6. To investigate effects of SBT-020 on cognition and other CNS functions, using the NeuroCart test battery. 7. To investigate effects of SBT-020 on motor functioning, using the NeuroCart test battery and unified Huntington’s disease rating scale. | |
| **Methodology:**  This study was a single-center, randomized, double-blind, placebo-controlled, 2 Part study, in which Part 1 was a multiple ascending dose finding study and Part 2 was a multiple dose study. The total duration of the study for each subject was approximately 181 days divided over two parts.  **Part 1**:  24 mild to moderate HD patients, dose levels of 5 mg/day, 15 mg/day and 25 mg/day were administered once daily for 7 days (6 active and 2 placebo per cohort). Screening (including eligibility checks, safety assessments and 31P-MRS) was conducted between Day -90 and -1. Subjects were randomized on Day 1 of the study and were administered daily SC injections between Day 1 and Day 7 by a qualified medical professional, either in-patient or at the subject’s home. Safety assessments were conducted on all dosing days, including recording of adverse events. Full 24 hour PK profiles (plasma and urine) were conducted on Days 1 and 7 and additional blood samples for clinical safety laboratory panels and harvesting of PBMCs (for assessment of MMP) were taken at the same timepoints. Subjects attended for a post-dose 31P-MRS on Day 7. A follow-up visit was conducted at Day 21 and concluded the subject’s participation in Part 1.  The wash-out period between Part 1 and 2 was at least 28 days.  **Part 2**:  23 mild to moderate HD patients who participated in Part 1, a dose level of 25mg/day was administered once daily for 28 days (11 active and 12 placebo). On Day -1 of Part 2, subjects were reassessed for continuing eligibility (including safety assessments and 31P-MRS). Subjects were randomized on Day 1 of Part 2 and were administered daily SC injections between Day 1 and Day 28 by a qualified medical professional, either in-patient or at the subject’s home. Safety assessments were conducted on all dosing days, including recording of adverse events. Peak and trough plasma PK samples were collected on Days 1, 7, 14 and 21 and additional blood samples for clinical safety laboratory panels were taken on the same days. Subjects attended as in-patients on Days 27 and 28 full safety and PD assessments including 31P-MRS. A follow-up visit was conducted at Day 42 and concluded the subject’s participation in the study. | |
| **Number of Subjects (Planned and Analyzed):**  Part 1: A total of 24 subjects were randomized to 3 dosing cohorts.  Part 2: A total of 24 subjects were to be enrolled in Part 2 however, one subject did not continue into the second part of the study. 23 subjects were analyzed in Part 2. | |
| **Diagnosis and Main Criteria for Inclusion and Exclusion:**  Male and female subjects aged at least 18 years with a DNA confirmed diagnosis (CAG expansion of 36 or more repeats in the HTT gene) of HD. HD was to be considered early stage (Unified Huntington’s Disease Rating Scale [UHDRS] Total Motor Score ≥ 5, UHDRS Total Functional Capacity Score ≥ 7, τPCr ≥ 32.4 s by 31P-MRS of skeletal muscle). Other eligibility criteria focused on the general well-being of the subjects and their suitability for participation in a clinical study. | |
| **Investigational Medicinal Product (IMP), Dose and Mode of Administration, Batch Number:**  SBT-020: Supplied as lyophilized powder (44 mg/vial) for reconstitution with sterile saline for injection.  SBT-020 was administered as a once daily SC injection.  SBT-020 Lot number: P04915 | |
| **Placebo, Dose and Mode of Administration, Batch Number:**  The placebo for this trial was composed of sterile saline for injection. The placebo was handled and administered identically to the active drug. | |
| **Duration of Treatment:**  Part 1: 7 days Part 2: 28 days | |
| **Criteria for Evaluation/Endpoints:**  **Safety Endpoints**  • Treatment emergent AEs  • Concomitant medication  • Change from baseline in clinical laboratory tests  • Change from baseline in vital signs parameters  • Change from baseline in ECG parameters  **Pharmacokinetic Endpoints**  **•** Plasma concentrations and PK parameters of SBT-020 and SBT-127 (tripeptide SBT-020-related component; Phe-D-Arg-Phe-OH)  • Urine concentrations and PK parameters of SBT-020 and SBT-098 (tetrapeptide SBT-020-related component; Phe-D-Arg-Phe-Lys-OH)  **Pharmacodynamic Endpoints**  Changes from baseline in:   * Phosphocreatine recovery time (seconds), measured by 31P-MRS in calf muscles * Difference between Pi/PCr ratio before and after visual stimulation, measured by 31P-MRS in the brain (Part 2 only) * Intensity of red-green fluorescence, measured by flow-cytometry in PBMCs * Mitochondrial membrane potential (ΔΨm) * Neuropsychological function (Part 2 only)   + Symbol Digit Modality Test (SDMT): Total number of correct responses in 90 seconds, Stroop color word interference test, Total number of correct responses in 45 seconds per trial   + Trail Making Test (TMT): Completion time in seconds per trial, Number of errors for each trial,   + Visual Verbal Learning Test (VVLT) memory testing: Immediate recall 1 (number correct), Immediate recall 2 (number correct), Immediate recall 3 (number correct), Delayed recall (number correct), Delayed recognition (number correct), and Delayed recognition (average reaction time correct) (msec).   + Sustained Attention to Response Task (SART) test: Total number of (commission and omission) errors, Mean reaction time of all correct response trials   + Adaptive tracking: Average performance (%); * Motor function (Part 2 only)   + Unified Huntington Disease Rating Scale (UHDRS)   + Total motor score (TMS): Total functional capacity score (TFC)   + Finger tapping test: Mean tapping rate (taps per second) and standard deviation,   + Saccadic eye movements: Saccadic reaction time (second), Saccadic peak velocity (degrees/second), and Saccadic inaccuracy (%);   + Smooth pursuit eye movements: Percentage of time the eyes of the subjects are in smooth pursuit of the target (%)   + Body sway: Antero-posterior sway (mm) | |
| **Statistical Methods:**  The following analysis populations were defined:  • Safety population: all study subjects who received at least one dose of study medication (subjects were analyzed according to the treatment they received).  • Pharmacokinetic population: all study subjects who received at least one dose of study medication and had at least one measurable drug concentration in samples analyzed.  • Pharmacodynamic population: all study subjects who received at least one dose of study medication and had at least one post-baseline assessment of the parameter reported.  All subjects treated in Part 1 (24 subjects) and Part 2 (23 subjects) were included in all analysis populations.  Generally, data were summarized using descriptive statistics (number of subjects, mean, median, standard deviation, minimum, and maximum) for continuous variables, and using frequencies and percentages for categorical variables. Data were presented by treatment group, as appropriate. Inferential testing, when performed, was 2-sided and tested at the alpha = 0.05 level of significance. All p-values, except for the primary analysis of the primary endpoint, were considered non-confirmatory.  To establish whether significant treatment effects was detected on the repeatedly measured PD parameters, each parameter has been analyzed with a mixed model analysis of covariance (ANCOVA) with treatment, time, and treatment by time as fixed factors, subject as a random factor and the baseline measurement as a covariate. Single measured PD parameters were analyzed with a mixed model ANCOVA with treatment as a fixed factor and the baseline measurement as a covariate. The Kenward-Roger approximation was used to estimate denominator degrees of freedom and model parameters were estimated using the restricted maximum likelihood method. The general treatment effect and specific contrasts was reported with the estimated difference and the 95% confidence interval, the least square mean estimates and the p-value. Graphs of the Least Squares Means (LSM) estimates over time by treatment were presented with 95% confidence intervals as error bars, as well as change from baseline LSM estimates.  Plasma pharmacokinetic parameters were derived by non-compartmental analysis of the plasma concentration data wherever appropriate:  Part 1, Day 1:  • Cmax: maximum observed concentration  • Tlag: the elapsed time from dosing at which SBT-020 is first quantifiable in a concentration vs time profile  • Tmax: the time from dosing at which Cmax was apparent AUC(0-last) area under the plasma concentration vs time curve from 0 time to last measurable concentration  • AUC(0-tau): the area under the concentration vs time curve within the dosing interval  Part 1, Day 7:  • Cmin,ss: the concentration minimum observed immediately prior to dose administration under steady state conditions  • Cmax,ss: maximum observed concentration under steady state conditions  • Cavg,ss: the average concentration within the dosing interval at steady state  • AUC(0-tau),ss: the area under the concentration vs time curve within the dosing interval  • AUC(0-last),ss: area under the plasma concentration vs time curve from 0 time to last measurable concentration  • AUC(0-inf),ss: area under the plasma concentration vs time curve from 0 time extrapolated to infinity  • AUC%extrap,ss: percentage of AUC(0–inf) extrapolated beyond last measured time point  • lambdaz,ss: the slope of the apparent elimination phase  • t½,ss: the apparent elimination half-life  • Vss/F: the apparent volume of distribution at steady state following an extravascular dose  Individual PK parameter data were listed for all individual patients and summary tables of parameters by treatment with, by point of measurement, the number of observations, mean, SD, median, Min, and Max, were made.  Urine pharmacokinetic parameters were derived, when relevant, as follows:  Part 1, Day 1:  • CLr: the apparent volume of plasma cleared of SBT-020 per unit time via renal elimination  • Ae: the amount of SBT-020 excreted in the urine  • Fe: the amount of SBT-020 eliminated in the urine over the collection period expressed as a percentage of the administered dose  Part 1, Day 7:  • CLr,ss: the apparent volume of plasma cleared of SBT-020 per unit time via renal elimination  • Ae,ss: the amount of SBT-020 excreted in the urine  • Fe,ss: the amount of SBT-020 eliminated in the urine over the collection period expressed as a percentage of the administered dose  Individual PK parameter data were listed for all individual patients and summary tables of parameters by treatment with, by point of measurement, the number of observations, mean, SD, median, Min, and Max, were made. | |
| **Summary Results:**  Demographics and Subject Disposition:  Part 1: A total of 24 subjects were enrolled (6 x 5 mg SBT-020, 6 x 15 mg SBT-020, 6 x 25 mg SBT-020 and 6 x placebo). All subjects completed Part 1 and were included in all analyses.  Part 2: A total of 23 subjects were enrolled (11 x 25 mg SBT-020 and 12 x placebo). All subjects completed Part 2 and were included in the analyses.  The same subjects were entered into both Parts 1 and 2 are therefore share demographics and baseline characteristics. The treatment groups were well matched overall with regards to demographic and other baseline characteristics. The median age of all subjects was 49 years (range 20 to 64 years). 11 (45.8%) females and 13 (54.2%) males were randomized. 23 subjects (95.8%) were White and 1 subject (4.2%) was reported as “mixed” race. Summary statistics across treatment groups were well-matched.  PD Results:  Part 1: SBT-020 at any dose level (5, 15 or 25 mg), administered once daily by SC injection for 7 days failed to demonstrate a difference (vs. placebo) in mitochondrial function assessed by 31P-MRS in skeletal muscle. A statistically significant treatment difference was observed vs. placebo (SBT-020 5 mg p = 0.0363; 15 mg p = 0.051; 25 mg p = 0.0310) in numbers of dysfunctional PBMCs. MMP was similar or increased following SBT-020 treatment compared to placebo, achieving statistical significance at SBT-020 25 mg (p = 0.0356).  Part 2: Overall, endpoints were not statistically significant where SBT-20 treatment was compared to placebo. Comparison of treatment effect in total errors in TMT visual scanning returned a p value of 0.0435 however, this is unlikely to be of clinical relevance.  PK Results: Part 1 summary SBT-020 plasma PK parameters are presented below:   | **Parameter** | **n** | **Mean** | **Median** | **SD** | **CV** | **Min** | **Max** | | --- | --- | --- | --- | --- | --- | --- | --- | | **SBT-020 5 mg – Day 1** |  | | | | | | | | Cmax (ng/ml) | 6 | 220.67 | 199.00 | 56.23 | 25.48 | 174.00 | 311.00 | | tmax (h) | 6 | 0.71 | 0.62 | 0.25 | 34.70 | 0.50 | 1.00 | | tlag (h) | 6 | 0.00 | 0.00 | 0.00 | NA | 0.00 | 0.00 | | AUC\_0\_last (ng\*h/ml) | 6 | 866.02 | 861.47 | 221.21 | 25.54 | 601.29 | 1203.44 | | **SBT-020 5 mg – Day 7** |  | | | | | | | | Cmax (ng/ml) | 6 | 214.50 | 211.50 | 55.14 | 25.71 | 132.00 | 276.00 | | AUC\_0\_last (ng\*h/ml) | 6 | 872.58 | 817.12 | 279.30 | 32.01 | 597.96 | 1325.97 | | AUC\_0\_inf (ng\*h/ml) | 6 | 940.75 | 882.24 | 281.19 | 29.89 | 653.23 | 1342.77 | | PercAUCExtrap (%) | 6 | 7.56 | 7.94 | 3.63 | 48.01 | 1.25 | 12.50 | | Lambda\_z (h-1) | 6 | 0.23 | 0.23 | 0.03 | 14.98 | 0.17 | 0.26 | | t½ (h) | 6 | 3.13 | 2.99 | 0.55 | 17.61 | 2.70 | 4.17 | | V\_F (L) | 6 | 25.04 | 23.98 | 5.02 | 20.06 | 19.65 | 32.05 | | **SBT-020 15 mg – Day 1** |  | | | | | | | | Cmax (ng/ml) | 6 | 833.00 | 886.50 | 169.89 | 20.40 | 603.00 | 1020.00 | | tmax (h) | 6 | 0.76 | 0.75 | 0.21 | 27.58 | 0.50 | 1.00 | | tlag (h) | 6 | 0.00 | 0.00 | 0.00 | NA | 0.00 | 0.00 | | AUC\_0\_last (ng\*h/ml) | 6 | 3700.87 | 3374.82 | 942.05 | 25.45 | 2770.29 | 5260.16 | | **SBT-020 15 mg – Day 7** |  | | | | | | | | Cmax (ng/ml) | 6 | 738.17 | 726.00 | 165.63 | 22.44 | 494.00 | 956.00 | | AUC\_0\_last (ng\*h/ml) | 6 | 3572.60 | 3301.97 | 733.75 | 20.54 | 2660.93 | 4510.37 | | AUC\_0\_inf (ng\*h/ml) | 6 | 3612.69 | 3332.43 | 743.28 | 20.57 | 2704.67 | 4583.36 | | PercAUCExtrap (%) | 6 | 1.11 | 0.91 | 0.39 | 35.11 | 0.80 | 1.62 | | Lambda\_z (h-1) | 6 | 0.18 | 0.18 | 0.01 | 6.89 | 0.16 | 0.19 | | t½ (h) | 6 | 3.94 | 3.90 | 0.28 | 7.00 | 3.64 | 4.31 | | V\_F (L) | 6 | 24.51 | 24.40 | 5.82 | 23.75 | 17.78 | 34.45 | | **SBT-020 25 mg Day 1** |  | | | | | | | | Cmax (ng/ml) | 6 | 1031.33 | 973.00 | 165.33 | 16.03 | 858.00 | 1310.00 | | tmax (h) | 6 | 0.76 | 0.75 | 0.23 | 30.62 | 0.50 | 1.03 | | tlag (h) | 6 | 0.00 | 0.00 | 0.00 | NA | 0.00 | 0.00 | | AUC\_0\_last (ng\*h/ml) | 6 | 4725.66 | 4618.57 | 489.18 | 10.35 | 4241.35 | 5475.74 | | **SBT-020 25 mg Day 7** |  | | | | | | | | Cmax (ng/ml) | 6 | 1176.17 | 1135.00 | 240.00 | 20.41 | 897.00 | 1610.00 | | AUC\_0\_last (ng\*h/ml) | 6 | 5252.10 | 5220.46 | 396.11 | 7.54 | 4805.33 | 5754.24 | | AUC\_0\_inf (ng\*h/ml) | 6 | 5321.96 | 5267.38 | 396.52 | 7.45 | 4871.52 | 5801.97 | | PercAUCExtrap (%) | 6 | 1.32 | 1.18 | 0.54 | 41.27 | 0.79 | 1.99 | | Lambda\_z (h-1) | 6 | 0.17 | 0.17 | 0.02 | 8.99 | 0.15 | 0.18 | | t½ (h) | 6 | 4.14 | 4.00 | 0.39 | 9.38 | 3.80 | 4.68 | | V\_F (L) | 6 | 28.20 | 27.77 | 3.69 | 13.08 | 23.64 | 34.08 |   Abbreviations: Cmax = maximum concentration, tmax = time to maximum concentration, tlag = time from dose to appearance of measurable plasma concentration, AUC0-last = area under the curve from time of dosing to last plasma sample collection timepoint, AUC0-inf = area under the curve from the time of dosing to infinity, PercAUCExtrap = percentage of AUC0-inf extrapolated from available plasma concentration data, Lambda z = estimate of the terminal elimination rate constant, t½ = terminal half-life, V = volume of distribution, F = bioavailability, SD = standard deviation, CV = coefficient of variance, min = minimum, max = maximum  SBT-020 was rapidly distributed as expected with parenteral administration. Tmax was achieved within one hour of dosing at all dose levels with Cmax and AUC0-last appearing to be dose-related and approximately linear between 5 and 25 mg/day. Apparent clearance and t½ were relatively stable across dose levels. Analysis of SBT-127 demonstrated a low level of metabolism (<2% parent) and confirmed previous data demonstrating that SBT-127 is not a major metabolite of SBT-020 in humans.  Urine PK confirmed previous data indicating that SBT-020 excretion in the 24 hours following dosing occurs primarily via renal mechanisms and the parent drug is largely unchanged. Mean fraction of compounds excreted in the urine on within the 24 hours following dosing on Day 1 were between 29.5% and 43.7% for SBT-020, between 6.41% and 7.03% for SBT-098 and 3.68% and 5.37% for SBT-127.  Safety Results:  Part 1: Once daily SC administration of SBT-020 at doses of 5 mg, 15 mg and 25 mg were generally safe and well tolerated in subjects with early stage HD during the 7-day repeat dose study. SBT-020 was not associated with a higher percentage of moderate or severe TEAEs, but local intolerance reactions were more common in the SBT-020 group than in the placebo treated subjects.  • The overall incidence of subjects who experienced at least 1 TEAE during the study was higher in all SBT-020 groups (100% of subjects) compared with the placebo group (83.3% of subjects).  • The most common TEAEs in the both SBT-020 and placebo treatment groups were all injection site related, including injection site erythema (all SBT-020 groups 100%; placebo 33.3%), injection site swelling (SBT-020 5 mg 50.0%; SBT-020 15 mg 66.7%; SBT-020 25 mg 83.3%; placebo 0%), and injection site pruritus (SBT-020 5 mg 0%; SBT-020 15 mg 33.3%; SBT-020 25 mg 83.3%; placebo 0%).  • One subject in the SBT-020 15 mg group experienced SAEs of pneumonia (68 days post-last-dose) and pulmonary embolism (84 days post-last dose) following successfully completing Part 1 of the study, considered unrelated to study treatment. There were no deaths or discontinuations due to TEAEs in any dosing group.  • One subject in the SBT-020 25 mg group experienced a severe TEAE (infection [in the shoulder region]) 11 days after completing Part 1 without incident. The TEAE was considered unlikely to related to study treatment.  • TEAEs considered by the Investigator to be to be related to study treatment were reported more frequently for subjects in the SBT-020 groups (all SBT-020 groups 100%) compared with the placebo group (83.3%), driven primarily by injection site reaction related events.  • Analyses of clinical laboratory data and other safety data (vital signs and ECGs) did not identify any clinically relevant findings associated with SBT-020 treatment.  Part 2: Once daily SC administration of SBT-020 at 25 mg was generally safe and well tolerated in subjects with early stage HD during the 28-day repeat dose study. SBT-020 was not associated with a higher percentage of moderate or severe TEAEs, but local intolerance reactions were more common in the SBT-020 group than in the placebo treated subjects.  • The overall incidence of subjects who experienced at least 1 TEAE during the study was slightly higher in all SBT-020 group (100% of subjects) compared with the placebo group (91.7% of subjects).  • The most common TEAEs in the both SBT-020 and placebo treatment groups were all injection site related, including injection site erythema (SBT-020 100%; placebo 58.3%), injection site swelling (SBT-020 81.8%; placebo 16.7%), and injection site pruritus (SBT-020 45.5%; placebo 8.3%).  • There were no SAEs, deaths or discontinuations due to TEAEs in either dosing group.  • TEAEs considered by the Investigator to be to be related to study treatment were reported more frequently for subjects in the SBT-020 group (100%) compared with the placebo group (58.3%), driven primarily by injection site reaction related events.  • Analyses of clinical laboratory data and other safety data (vital signs and ECGs) did not identify any clinically relevant findings associated with SBT-020 treatment.  Conclusion:   * Part 1   + SBT-020 at any dose level (5, 15 or 25 mg), administered once daily by SC injection for 7 days failed to demonstrate a difference (vs. placebo) in mitochondrial function assessed by 31P-MRS in skeletal muscle. A statistically significant treatment difference was observed vs. placebo (SBT-020 5 mg p = 0.0363; 15 mg p = 0.051; 25 mg p = 0.0310) in numbers of dysfunctional PBMCs. MMP was similar or increased following SBT-020 treatment compared to placebo, achieving statistical significance at SBT-020 25 mg (p = 0.0356).   + SBT-020 is rapidly distributed following SC administration and does not demonstrate significant metabolism in humans. Tmax was achieved within one hour of dosing at all dose levels with Cmax and AUC0-last appearing to be dose-related and approximately linear between 5 and 25 mg/day. Apparent clearance and t½ were relatively stable across dose levels.   + SBT-020 was not associated with a higher percentage of TEAEs with the exception of local injection site reactions. The most common TEAEs in the both SBT-020 and placebo treatment groups were all injection site related, including injection site erythema (all SBT-020 groups 100%; placebo 33.3%), injection site swelling (SBT-020 5 mg 50.0%; SBT-020 15 mg 66.7%; SBT-020 25 mg 83.3%; placebo 0%), and injection site pruritus (SBT-020 5 mg 0%; SBT-020 15 mg 33.3%; SBT-020 25 mg 83.3%; placebo 0%).   + Analyses of clinical laboratory data and other safety data (vital signs and ECGs) did not identify any clinically relevant findings associated with SBT-020 treatment. * Part 2   + SBT-020 25 mg, administered once daily by SC injection for 28 days failed to demonstrate a difference (vs. placebo) in mitochondrial function assessed by either 31P-MRS in skeletal muscle and brain tissue or PBMC function changes and MMP.   + SBT-020 25 mg, administered once daily by SC injection for 28 days failed to demonstrate a difference (vs. placebo) in neurological or functional assessments.   + SBT-020 was not associated with a higher percentage of TEAEs, with the exception of local injection site reactions. The most common TEAEs in the both SBT-020 and placebo treatment groups were all injection site related, including injection site erythema (SBT-020 100%; placebo 58.3%), injection site swelling (SBT-020 81.8%; placebo 16.7%), and injection site pruritus (SBT-020 45.5%; placebo 8.3%).   + Analyses of clinical laboratory data and other safety data (vital signs and ECGs) did not identify any clinically relevant findings associated with SBT-020 treatment. | |
| **Date and Version of Report:**  Final CSR, 05 October 2021 | |